Synthesis of Dialkyl 2-(Alkylamino)-4,9-dihydro-9-oxocyclohepta[*b*]pyran-3,4-dicarboxylates

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Dialkyl 2-(alkylamino)-4,9-dihydro-9-oxocyclohepta[*b*]pyran-3,4-dicarboxylates are prepared in a one-pot three-component reaction of alkyl isocyanide, dialkyl acetylenedicarboxylate, and α-tropolone (=2-hydroxycyclohepta-2,4,6-trienone). The reaction proceeds smoothly at room temperature and under neutral conditions to afford tropolone derivatives in high yield.

Introduction. – Heterocycle-fused tropolones, an important class of compounds with varied pharmacological and biological properties have attracted great attention since the beginning of tropoid chemistry [1–4]. The cyclohepta[*b*]pyran ring system is the backbone of some natural products such as paulitine (*Fig.*), which displays several biological activities, and some derivatives of this system exhibit platelet anti-aggregating, HIV protease inhibition, anesthetic, histaminic response-reducing, antimalarial, anti-inflammatory, and analgesic activities [5–8]. Only a few methods have been reported for the construction of cyclohepta[*b*]pyran ring systems. In a first method, a cyclohepta[*e*][1,3,2]dioxaborin ring is formed by reaction of cycloheptanone with Ac_2O in presence of BF_3, and subsequent reaction with *Vilsmeier* reagent provides the cyclohepta[*b*]pyran system [6]. In a second method, reaction of 3-acetyltropolone with benzaldehydes yields 3-cinnamoyltropolones, which are cyclized to 2-arylcyclohepta[*b*]pyran-4,9-diones in presence of oxidizing reagents such as SeO_2 [9], 2,3-dichloro-5,6-dicyano-1,4-benzoquinone [10], $HClO_4$ [11], Br_2 [12], and I_2/DMSO/H_2SO_4 [13]. Also the reaction of chloro(phenyl)ketene with 2-(aminomethylidene)cycloheptanones, followed by dehydrochlorination of the primary adducts, yields 4-amino-6,7,8,9-tetrahydro-3-phenylcyclohepta[*b*]pyran-2(5*H*)-ones [14].

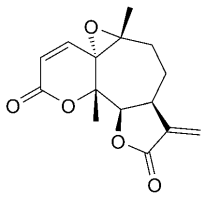
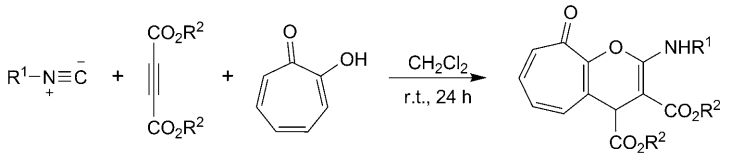


Figure. *Molecular structure of paulitine* (see text)

In continuation of our previous studies on the development of new routes to heterocyclic systems (see [15] and refs. cit. therein), we now report an efficient and facile synthetic route to dialkyl 2-(alkylamino)-4,9-dihydro-9-oxocyclohepta[*b*]pyran-3,4-dicarboxylates **4** using α-tropolone (=2-hydroxycyclohepta-2,4,6-trienone; **3**), alkyl isocyanides **1**, and dialkyl acetylenedicarboxylates **2** without any catalyst (*Scheme 1*).

Scheme 1. *Synthesis of Tropolone Derivatives* **4** *from Alkyl Isocyanide* **1**, *Dialkyl Acetylenedicarboxylate* **2**, *and Tropolone* (**3**)



1 **2** **3**

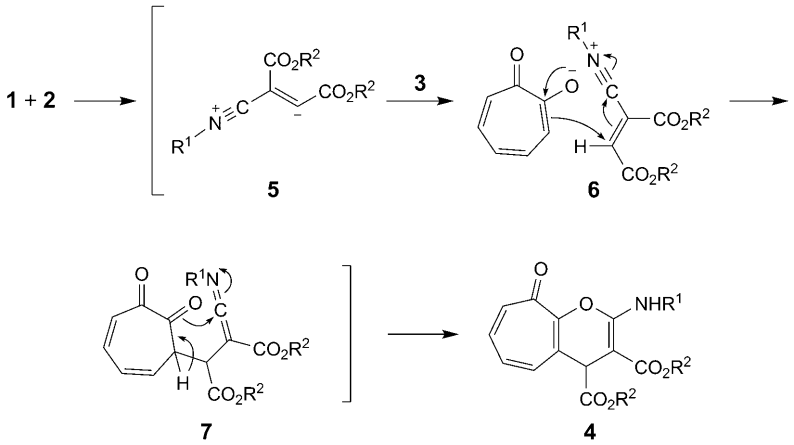
	R^1	R^2	Yield [%]
4a	Cyclohexyl	Me	86
4b	Cyclohexyl	Et	83
4c	*t*-Bu	Me	81
4d	*t*-Bu	Et	80
4e	1,1,3,3-Tetramethylbutyl	Me	80
4f	1,1,3,3-Tetramethylbutyl	Et	79
4g	Cyclohexyl	*t*-Bu	65

Results and Discussion. – The three-component reaction of alkyl isocyanide **1**, dialkyl acetylenedicarboxylate **2**, and **3** proceeded in CH_2Cl_2 at ambient temperature and was completed after 24 h to afford dialkyl 2-(alkylamino)-4,9-dihydro-9-oxocyclohepta[*b*]pyran-3,4-dicarboxylates **4** in yields of 65–86% (*Scheme 1*).

The structures of the products **4a**–**4g** were deduced from their IR, ^{1}H- and ^{13}C-NMR, and MS data. For example, the mass spectrum of **4a** displayed the molecular-ion peak at 373 *m*/*z*, which is consistent with a 1:1:1 adduct of **1a**, **2a**, and **3**. The ^{1}H-NMR spectrum of **4a** exhibited a *multiplet* for the cyclohexyl substituent (δ(H) 1.16–2.07), two *singlet*s for two MeO groups (δ(H) 3.63 and 3.68), a *multiplet* for $(CH_2)_5CH$–N (δ(H) 3.99), a *singlet* for H–C(4) (δ(H) 4.55) and two *multiplet*s for three H-atoms of the tropone ring (δ(H) 6.83–6.91 and δ(H) 7.12–7.20), and a *doublet* (δ(H) 7.06, ^3J = 11.2), as well as a broad *singlet* for NH (δ(H) 8.26). The ^{1}H-decoupled ^{13}C-NMR spectrum of **4a** showed 20 distinct resonances, partial assignments of these resonances is given in the *Exper. Part*. The ^{1}H- and ^{13}C-NMR spectra of **4b**–**4g** are similar to those of **4a**, except for *N*-alkyl and esters moieties.

Although the mechanism of this reaction has not been established experimentally, a reasonable proposal is depicted in *Scheme 2*. On the basis of isocyanide chemistry [16], the zwitterionic intermediate **5** from reaction of alkyl isocyanide **1** and dialkyl acetylenedicarboxylate **2** is protonated by OH of **3**. Subsequent reaction of the nitrilium ion **6** with the deprotonated tropolone produces ketenimine **7**. This addition product may tautomerize and then cyclize, under the employed reaction conditions, to form tropolone derivatives **4**.

Scheme 2. *Proposed Mechanism for the Formation of Tropolone Derivatives* **4**



Conclusions. – We have developed a new and efficient synthetic method for the preparation of dialkyl 2-(alkylamino)-4,9-dihydro-9-oxocyclohepta[*b*]pyran derivatives. The present method has the advantage that the reaction is performed under neutral conditions with easily available starting materials to give high yields.

Experimental Part

General. Starting materials and solvents were obtained from *Merck* (Germany) and *Fluka* (Switzerland), and were used without further purification. Column chromatography (CC): *Merck* silica-gel powder. M.p.: *Electrothermal 9100* apparatus; uncorrected. IR Spectra: *Shimadzu IR-460* spectrometer; in KBr. ^{1}H- and ^{13}C-NMR spectra ($CDCl_3$ soln.): *BRUKER DRX-250 AVANCE* spectrometer at 250.0, and 62.9 MHz, resp. MS: *Agilent-Technologies-(HP)-5973* mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses: *Heraeus CHN-O-Rapid* analyzer.

General Procedure for the Preparation of Compounds **4**. To a magnetically stirred soln. of *tropolone* (**3**, 1 mmol) and dialkyl acetylenedicarboxylate **2** (1 mmol) in dry CH_2Cl_2 (5 ml) was added a soln. of alkyl isocyanide **1** (1 mmol) in dry CH_2Cl_2 (2 ml). The mixture was stirred for 24 h. The solvent was evaporated, and the residue was purified by CC using petroleum ether/AcOEt mixtures.

*Dimethyl 2-(Cyclohexylamino)-4,9-dihydro-9-oxocyclohepta[*b*]pyran-3,4-dicarboxylate* (**4a**). Yield 320 mg (86%). Brown semisolid. IR: 3292 (NH), 2924, 1744, 1684, 1620, 1441, 1269, 1084. ^{1}H-NMR: 1.16–2.07 (*m*, 5 CH_2 of cyclohexyl); 3.63 (*s*, MeO); 3.68 (*s*, MeO); 3.90–4.11 (*m*, N–CH); 4.55 (*s*, CH); 6.83–6.91 (*m*, 1 H of tropone); 7.06 (*d*, J = 11.2, 1 H of tropone); 7.12–7.20 (*m*, 2 H of tropone); 8.26 (br. *s*, NH). ^{13}C-NMR: 24.40, 24.45, 25.47, 33.44, 33.62 (5 CH_2 of cyclohexyl); 45.52 (CH); 50.20 (CH–NH); 50.94, 52.73 (2 MeO); 70.22, 125.66, 130.34, 135.37, 135.97, 139.57, 154.67, 159.46 (C of alkene and tropone); 168.53, 172.32, 177.87 (3 C=O). EI-MS: 373 (2, M^+), 314 (100, $[M - CO_2Me]^+$), 232 (48, $[314 - C_6H_{10}]^+$), 200 (14, $[M + H - CO_2Me - C_6H_{10} - MeO]^+$), 172 (19, $[200 - CO]^+$), 157 (9, $[172 - NH_2]^+$). Anal. calc. for $C_{20}H_{23}NO_6$ (373.40): C 64.33, H 6.21, N 3.75; found: C 64.26, H 6.13, N 3.68.

*Diethyl 2-(Cyclohexylamino)-4,9-dihydro-9-oxocyclohepta[*b*]pyran-3,4-dicarboxylate* (**4b**). Yield 330 mg (83%). Brown semisolid. IR: 3281 (NH), 2932, 1737, 1682, 1616, 1440, 1229, 1086. ^{1}H-NMR: 1.15 (*t*, J = 7.0, Me); 1.22 (*t*, J = 7.2, Me); 1.23–2.10 (*m*, 5 CH_2 of cyclohexyl); 3.90–4.00 (*m*, N–CH); 3.99–4.20 (*m*, 2 CH_2O); 4.51 (*s*, CH); 6.80–6.92 (*m*, 1 H of tropone); 7.07 (*d*, J = 11.40, 1 H of tropone); 7.12–7.31 (*m*, 2 H of tropone); 8.25 (br. *s*, NH). ^{13}C-NMR: 14.07, 14.56 (2 Me); 24.40, 24.42, 25.48, 33.45,

33.59 (5 CH_2 of cyclohexyl); 45.65 (CH); 50.11 (CH–NH); 59.36, 61.47 (2 CH_2O); 70.34, 125.59, 130.16, 135.38, 135.95, 139.48, 154.58, 159.22 (C of alkene and tropone); 168.23, 172.00, 177.93 (3 C=O). EI-MS: 401 (1, M^+), 328 (100, $[M - CO_2Et]^+$), 246 (46, $[328 - C_6H_{10}]^+$), 218 (12, $[246 - Et]^+$), 200 (12, $[246 - EtO]^+$), 172 (15, $[200 - CO]^+$), 157 (6, $[172 - NH_2]^+$). Anal. calc. for $C_{22}H_{27}NO_6$ (401.46): C 65.82, H 6.78, N 3.49; found: C 65.73, H 6.83, N 3.34.

*Dimethyl 2-(*tert*-Butylamino)-4,9-dihydro-9-oxocyclohepta[*b*]pyran-3,4-dicarboxylate* (**4c**). Yield 280 mg (81%). Yellow powder. M.p. 115–117°. IR: 3314 (NH), 2954, 1731, 1676, 1616, 1430, 1166, 1081. ^{1}H-NMR: 1.51 (*s*, *t*-Bu); 3.65, 3.69 (2*s*, 2 MeO); 4.56 (*s*, CH); 6.83–6.94 (*m*, 1 H of tropone); 7.07 (*d*, J = 11.5, 1 H of tropone); 7.11–7.21 (*m*, 2 H of tropone); 8.51 (br. *s*, NH). ^{13}C-NMR: 29.95 (3 Me); 45.32 (CH); 51.01, 52.77 (2 MeO); 53.16 (C–NH); 70.70, 125.35, 130.35, 135.44, 135.91, 139.66, 154.67, 160.54 (C of alkene and tropone); 168.71, 172.38, 177.82 (3 C=O). EI-MS: 347 (2, M^+), 288 (56, $[M - CO_2Me]^+$), 232 (100, $[288 - Me_2CCH_2]^+$), 200 (17, $[232 - MeO]^+$), 172 (23, $[200 - CO]^+$), 157 (9, $[172 - NH_2]^+$). Anal. calc. for $C_{18}H_{21}NO_6$ (347.37): C 62.24, H 6.09, N 4.03; found: C 62.32, H 5.91, N 3.92.

*Diethyl 2-(*tert*-Butylamino)-4,9-dihydro-9-oxocyclohepta[*b*]pyran-3,4-dicarboxylate* (**4d**). Yield 300 mg (80%). Yellow powder. M.p. 118–120°. IR: 3260 (NH), 2979, 1733, 1673, 1613, 1433, 1185, 1087. ^{1}H-NMR: 1.160 (*t*, J = 7.0, Me); 1.22 (*t*, ^3J = 7.2, Me); 1.48 (*s*, *t*-Bu); 4.01–4.20 (*m*, 2 CH_2O); 4.51 (*s*, CH); 6.79–6.92 (*m*, 1 H of tropone); 7.06 (*d*, J = 11.6, 1 H of tropone); 7.11–7.18 (*m*, 2 H of tropone); 8.49 (br. *s*, NH). ^{13}C-NMR: 14.06, 14.55 (2 Me); 29.93 (3 Me); 45.47 (CH); 53.01 (C–NH); 59.41, 61.47 (2 CH_2O); 70.82, 125.30, 130.17, 135.42, 135.88, 139.55, 154.59, 160.31 (C of alkene and tropone); 168.34, 172.04, 177.84 (3 C=O). EI-MS: 375 (1, M^+), 302 (59, $M - CO_2Et]^+$), 246 (100, $[302 - Me_2CCH_2]^+$), 218 (10, $[246 - Et]^+$), 200 (12, $[246 - EtO]^+$), 172 (17, $[200 - CO]^+$), 157 (6, $[172 - NH_2]^+$). Anal. calc. for $C_{20}H_{25}NO_6$ (375.42): C 63.99, H 6.71, N 3.73; found: C 64.12, H 6.83, N 3.61.

*Dimethyl 4,9-Dihydro-9-oxo-2-[(1,1,3,3-tetramethylbutyl)amino]cyclohepta[*b*]pyran-3,4-dicarboxylate* (**4e**). Yield 330 g (80%). Yellow powder. M.p. 156–158°. IR: 3380 (NH), 2947, 1727, 1669, 1604, 1436, 1161, 1079. ^{1}H-NMR: 0.99 (*s*, Me_3C); 1.56 (*s*, Me_2C); 1.95 (*AB*, J = 15.6, CH_2); 3.65, 3.70 (*s*, 2 MeO); 4.57 (*s*, CH); 6.83–6.95 (*m*, 1 H of tropone); 7.08 (*d*, J = 11.2, 1 H of tropone); 7.12–7.24 (*m*, 2 H of tropone); 8.57 (br. *s*, NH). ^{13}C-NMR: 30.65, 30.98 (2 Me); 31.41 (Me_3C); 31.60 (C); 45.43 (CH); 50.97 (MeO); 52.20 (CH_2); 52.71 (MeO); 56.63 (C–NH); 70.38, 125.40, 130.33, 135.42, 135.87, 139.68, 154.59, 160.42 (C of alkene and tropone); 168.74, 172.43, 177.74 (3 C=O). EI-MS: 401 (1, $[M - 2]^+$), 344 (9, $[M - CO_2Me]^+$), 328 (100, $[344 - Me]^+$), 246 (40, $[344 - C_7H_{14}]^+$), 232 (31, $[246 - Me]^+$), 200 (15, $[232 - MeO]^+$), 172 (17, $[200 - CO]^+$), 157 (8, $[172 - NH_2]^+$). Anal. calc. for $C_{22}H_{29}NO_6$ (403.48): C 65.49, H 7.24, N 3.47; found: C 65.38, H 7.32, N 3.58.

*Diethyl 4,9-Dihydro-9-oxo-2-[(1,1,3,3-tetramethylbutyl)amino]cyclohepta[*b*]pyran-3,4-dicarboxylate* (**4f**). Yield 340 mg (79%). Yellow powder. M.p. 154–156°. IR: 3269 (NH), 2952, 1727, 1669, 1615, 1434, 1177, 1082. ^{1}H-NMR: 0.96 (*s*, Me_3C); 1.160 (*t*, J = 7.0, Me); 1.23 (*t*, J = 7.0, Me); 1.53 (*s*, Me_2C); 1.92 (*AB*, J = 14.2, CH_2); 4.01–4.17 (*m*, 2 CH_2O); 4.52 (*s*, CH); 6.80–6.92 (*m*, 1 H of tropone); 7.08 (*d*, J = 11.6, 1 H of tropone); 7.11–7.19 (*m*, 2 H of tropone); 8.58 (br. *s*, NH). ^{13}C-NMR: 14.07, 14.55, 30.71, 30.96 (4 Me); 31.42 (Me_3C); 31.60 (C); 45.60 (CH); 52.11 (CH_2); 56.48 (C–NH); 59.35, 61.43 (2 CH_2O); 70.53, 125.30, 130.13, 135.41, 135.84, 139.57, 154.56, 160.13 (C of alkene and tropone); 168.41, 172.08, 177.77 (3 C=O). EI-MS: 431 (1, M^+), 358 (29, $[M - CO_2Et]^+$), 328 (4, $[358 - 2\,Me]^+$), 246 (100, $[358 - CMe_2CH_2CMe_3]^+$), 218 (9, $[246 - Et]^+$), 200 (15, $[246 - EtO]^+$), 172 (19, $[200 - CO]^+$), 157 (8, $[172 - NH_2]^+$). Anal. calc. for $C_{24}H_{33}NO_6$ (431.53): C 66.80, H 7.71, N 3.24; found: C 66.92, H 7.64, N 3.31.

*Di(*tert*-butyl) 2-(Cyclohexylamino)-4,9-dihydro-9-oxocyclohepta[*b*]pyran-3,4-dicarboxylate* (**4g**). Yield 300 mg (65%). Yellow semisolid. IR: 3305 (NH), 2931, 1729, 1674, 1619, 1443, 1156, 1086. ^{1}H-NMR: 1.10–2.15 (*m*, 5 CH_2 of cyclohexyl); 1.38 (*s*, Me_3C); 1.48 (*s*, Me_3C); 3.87–4.04 (*m*, H–C–N); 4.35 (*s*, CH); 6.81–6.92 (*m*, 1 H of tropone); 7.12 (*d*, J = 11.3, 1 H of tropone); 7.13–7.25 (*m*, 2 H of tropone); 8.18 (br. *s*, NH). ^{13}C-NMR: 24.73, 25.56 (2 CH_2 of cyclohexyl); 27.89 (Me_3C); 27.99 (CH_2); 28.59 (Me_3C); 32.74, 33.77 (2 CH_2 of cyclohexyl); 47.23 (CH); 50.26 (CH–NH); 77.22, 79.31, 81.46 (2 C and C of alkene); 126.07, 129.68, 135.72, 135.85, 139.41, 154.18, 158.86 (C of alkene and tropone); 168.21, 171.35, 178.11 (3 C=O). EI-MS: 457 (1, M^+), 356 (29, $[M - CO_2t\text{-Bu}]^+$), 300 (100, $[356 - t\text{-Bu}]^+$), 218 (33, $[300 - C_6H_{10}]^+$), 57 (17, $[t\text{-Bu}]^+$). Anal. calc. for $C_{26}H_{35}NO_6$ (457.57): C 68.25, H 7.71, N 3.06; found: C 68.37, H 7.62, N 3.11.

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